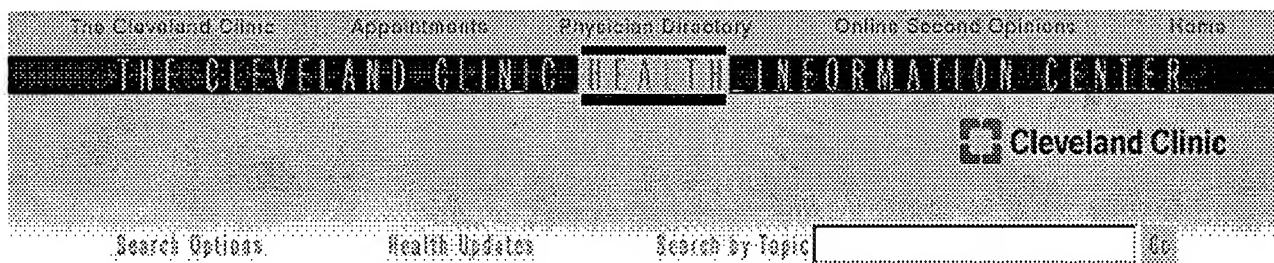


This is Google's cache of <http://www.clevelandclinic.org/health/health-info/docs/3600/3657.asp?index=12051> as retrieved on Aug 14, 2006 08:18:35 GMT.  
 Google's cache is the snapshot that we took of the page as we crawled the web.  
 The page may have changed since that time. Click here for the [current page](#) without highlighting.  
 This cached page may reference images which are no longer available. Click here for the [cached text only](#).  
 To link to or bookmark this page, use the following url: <http://www.google.com/search?q=cache:ezpRDRfEUIJ:www.clevelandclinic.org/health/health-info/docs/3600/3657.asp%3Findex%3D12051+cure+for+acute+chronic+pain&hl=en&gl=us&ct=clnk&cd=20>

*Google is neither affiliated with the authors of this page nor responsible for its content.*

These search terms have been highlighted: **cure acute chronic pain**



## Acute vs. Chronic Pain

### What is pain?

**Pain** is an uncomfortable feeling and/or an unpleasant sensation in the body. The presence of **pain** often is an indication that something is wrong. **Pain** can appear suddenly or can come about slowly.

Each individual is the best judge of his or her own **pain**. Feelings of **pain** can range from mild and occasional to severe and constant. **Pain** can be classified as **acute pain** or **chronic pain**.

### What is acute pain?

**Acute pain** begins suddenly and is usually sharp in quality. It serves as a warning of disease or a threat to the body. **Acute pain** might be caused by many events or circumstances, including:

- Surgery
- Broken bones
- Dental work
- Burns or cuts
- Labor and childbirth

**Acute pain** might be mild and last just a moment, or it might be severe and last for weeks or months. In most cases, **acute pain** does not last longer than six months, and it disappears when the underlying cause of **pain** has been treated or has healed. Unrelieved **acute pain**, however, might lead to **chronic pain**.

### What is chronic pain?

**Chronic pain** persists despite the fact that the injury has healed. **Pain** signals remain active in the nervous system for weeks, months, or years. Physical effects include tense muscles, limited mobility, a lack of energy, and changes in appetite. Emotional effects include

depression, anger, anxiety, and fear of re-injury. Such a fear might hinder a person's ability to return to normal work or leisure activities. Common **chronic pain** complaints include:

- Headache
- Low back **pain**
- Cancer **pain**
- Arthritis **pain**
- Neurogenic **pain** (**pain** resulting from damage to nerves)
- Psychogenic **pain** (**pain** not due to past disease or injury or any visible sign of damage inside)

**Chronic pain** might have originated with an initial trauma/injury or infection, or there might be an ongoing cause of **pain**. However, some people suffer **chronic pain** in the absence of any past injury or evidence of body damage.

#### What is the difference between acute and chronic pain?

- There might be no known **cure** for the disease (such as arthritis or phantom **pain**) that is causing the **chronic pain**.
- The cause of **chronic pain** might be unknown or poorly understood.

#### How is pain treated?

Depending upon its severity, **pain** might be treated in a number of ways. Symptomatic options for the treatment of **pain** might include one or more of the following:

- Non-steroidal anti-inflammatory drugs (NSAIDs), a specific type of painkiller such as Motrin or Aleve
- Acetaminophen (such as Tylenol)
- Narcotics (such as morphine or codeine)
- Localized anesthetic (a shot of a **pain** killer medicine into the area of the **pain**)
- Nerve blocks (the blocking of a group of nerves with local anesthetics)
- Acupuncture
- Electrical stimulation
- Physical therapy
- Surgery
- Psychotherapy (talk therapy)
- Relaxation techniques such as deep breathing
- Biofeedback (treatment technique in which people are trained to improve their health by using signals from their own bodies)
- Behavior modification

Some **pain** medicines are more effective in fighting **pain** when they are combined with other methods of treatment. Patients might need to try various methods to maintain maximum **pain** relief.

© Copyright 1995-2006 The Cleveland Clinic Foundation. All rights reserved

[Click here to go to the Pain Management Department Web site.](#)

[Know someone who could use this information?....send them this link.](#)



This is Google's cache of <http://www.webmd.com/content/article/100/105627.htm> as retrieved on Aug 27, 2006 13:31:23 GMT.

Google's cache is the snapshot that we took of the page as we crawled the web.

The page may have changed since that time. Click here for the current page without highlighting.

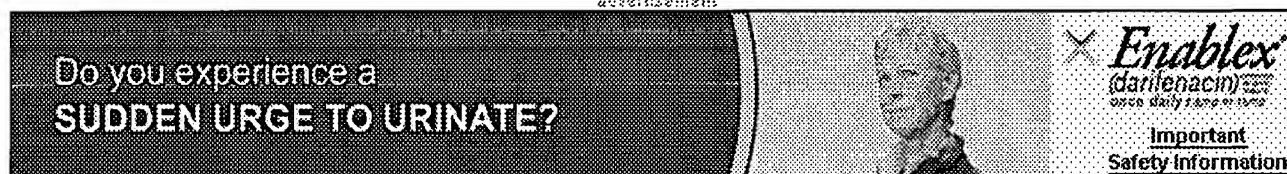
This cached page may reference images which are no longer available. Click here for the cached text only.

To link to or bookmark this page, use the following url: <http://www.google.com/search?q=cache:H02v-nDVnisJ:www.webmd.com/content/article/100/105627.htm+no+cure+pain&hl=en&gl=us&ct=clnk&cd=12>

Google is neither affiliated with the authors of this page nor responsible for its content.

These search terms have been highlighted: **no cure pain**

advertisement:



Do you experience a  
**SUDDEN URGE TO URINATE?**

**Enablex**  
(darifenacin)  
once daily 15 mg or 30 mg

**Important  
Safety Information**

August 29, 2006

SEARCH

Join Now | Sign In  
Bookmark This Page  
About the WebMD Redesign

HOME PAGE

TODAY'S NEWS

DISEASES & CONDITIONS

Health Centers Home

Check Your Symptoms

Women's Conditions

Men's Conditions

Ask an Expert

A-Z GUIDES

HEALTHY LIVING

HEALTH CARE SERVICES

PREGNANCY & FAMILY

BOARDS & BLOGS

FREE Newsletters Print Friendly Version Email a Friend

WebMD Medical Reference in collaboration with THE CLEVELAND CLINIC

## Pain Management: Complex Regional Pain Syndrome

Complex regional pain syndrome (CRPS), also called reflex sympathetic dystrophy syndrome, is a chronic pain condition in which high levels of nerve impulses are sent to an affected site. Experts believe that CRPS occurs as a result of dysfunction in the central or peripheral nervous systems.

CRPS is most common in people aged 20-35. The syndrome also can occur in children; it affects women more often than men.

There is **no cure** for CRPS.

### What Causes Complex Regional Pain Syndrome?

CRPS most likely does not have a single cause but rather results from multiple causes that produce similar symptoms. Some theories suggest that pain receptors in the affected part of the body become responsive

### Get the Facts

#### Types of Pain

- [Arachnoiditis](#)
- [Arthritis](#)
- [Rheumatoid Arthritis](#)
- [Osteoarthritis](#)
- [Burn Pain](#)
- [Cancer Pain](#)
- [Facial Pain](#)
- [Fibromyalgia](#)
- [Headaches](#)
- [Tension Headaches](#)
- [Cluster Headaches](#)
- [Migraine Headaches](#)
- [Spinal Headaches](#)
- [Musculoskeletal Pain](#)
- [Back Pain](#)
- [Neck and Shoulder Pain](#)
- [Whiplash](#)
- [Myofascial Pain Syndrome](#)
- [Neuropathic Pain](#)
- [Complex Pain Syndrome](#)
- [Central Pain Syndrome](#)
- [Postherpetic Neuralgia](#)
- [Phantom Limb Pain](#)
- [Diabetic Neuropathy](#)
- [Pelvic Pain](#)
- [Psychogenic Pain](#)
- [Sciatica](#)
- [Skin Disorders](#)
- [Shingles](#)
- [Herpes](#)
- [Skin Tumor & Cysts](#)
- [Scleroderma](#)
- [Neurofibromatosis](#)
- [Vasculitis](#)
- [Spasticity](#)
- [Spinal Cord Injury](#)
- [Sickle Cell Disease](#)

advertisement

to catecholamines, a group of nervous system messengers. In cases of injury-related CRPS, the syndrome may be caused by a triggering of the immune response which may lead to the inflammatory symptoms of redness, warmth, and swelling in the affected area. For this reason, it is believed that CRPS may represent a disruption of the healing process.

- [Spinal Stenosis](#)
- [Spondylolithesis](#)
- [Temporomandibular Disorders](#)
- [Vascular Disease](#)

Tests You Take

Treatments

Special Populations

Day-to-Day

Bookshelf

» [To Pain Management Health Center](#)

### What Are the Symptoms of Complex Regional Pain Syndrome?

The symptoms of CRPS vary in their severity and length. One symptom of CRPS is continuous, intense **pain** that gets worse rather than better over time. If CRPS occurs after an injury, it may seem out of proportion to the severity of the injury. Even in cases involving an injury only to a finger or toe, **pain** can spread to include the entire arm or leg. In some cases, **pain** can even travel to the opposite extremity. Other symptoms of CRPS include:

- "Burning" **pain**
- Swelling and stiffness in affected joints
- Motor disability, with decreased ability to move the affected body part
- Changes in nail and hair growth patterns. There may be rapid hair growth or **no** hair growth.
- Skin changes. CRPS involves changes in skin temperature – skin on one extremity can feel warmer or cooler compared to the opposite extremity. Skin color changes also are apparent as the skin is often blotchy, pale, purple or red. The texture of skin also can change, becoming shiny and thin. People with syndrome may have skin that sometimes is excessively sweaty.

CRPS may be heightened by emotional stress.

### How Is Complex Regional Pain Syndrome Diagnosed?

There is **no** specific diagnostic test for CRPS, but some testing can rule out other conditions. Triple-phase bone scans can be used to identify changes in the bone and in blood circulation. Some health care providers may apply a stimulus (for example, heat, touch, cold) to determine whether there is **pain** in a specific area.

Making a firm diagnosis of CRPS may be difficult early in the course of the disorder when symptoms are few or mild. CRPS is diagnosed primarily through observation of the following symptoms:

- The presence of an initial injury
- A higher-than-expected amount of **pain** from an injury
- A change in appearance of an affected area
- The presence of **no** other cause of **pain** or altered appearance

### How Is Complex Regional Pain Syndrome Treated?

Since there is **no** cure for CRPS, the goal of treatment is to relieve painful symptoms associated with the disorder. Therapies used include [psychotherapy](#), [physical therapy](#), and [drug treatment](#), such as topical analgesics, narcotics, corticosteroids, antidepressants and anti-seizure drugs.

advertisement

**DO YOU  
NEED TO  
LOSE  
WEIGHT?**

FIND YOUR WEIGHT »

HEIGHT	AGE 19-34	AGE OVER 35
5'0"	97 - 129	108 - 139
5'1"	101 - 132	111 - 143
5'2"	104 - 137	115 - 148

**Lose 10 Lbs.  
in 5 weeks**

Height:

5 ft 7 in.

Weight:

lbs.

Age:

**FREE! eDiets Profile**

BODY SHAPING REQUIRES DIET & EXERCISE. \*CLICK FOR DETAILS

advertisement

Other treatments include:

- **Sympathetic nerve blocks:** These blocks, which are done in a variety of ways, can provide significant pain relief for some people. One kind of block involves placing an anesthetic next to the spine to directly block the sympathetic nerves.
- **Surgical sympathectomy:** This controversial technique destroys the nerves involved in CRPS. Some experts believe it has a favorable outcome, while others feel it makes CRPS worse. The technique should be considered only for people whose pain is dramatically but temporarily relieved by selective sympathetic blocks.
- **Intrathecal drug pumps:** Pumps and implanted catheters are used to send pain-relieving medication into the spinal fluid.
- **Spinal cord stimulation:** This technique, in which electrodes are placed next to the spinal cord, offers relief for many people with the condition.

Get tips on how to better cope with chronic pain.

View the full table of contents for the Pain Management Guide.

Reviewed by the doctors at The Cleveland Clinic Pain Management Department.

Edited by Charlotte E. Grayson, MD, WebMD, June 2004.

Portions of this page © The Cleveland Clinic 2000-2005

#### WebMD Health Centers

⊙ = Sponsored Resources ▶ = WebMD Health Center

▶ <b>Cancer</b>	▶ <b>Children's Health</b>	▶ <b>Depression</b>	▶ <b>Diabetes</b>	▶ <b>Diet &amp; Nutrition</b>
▶ <b>Heart Health</b>	▶ <b>Men's Health</b>	▶ <b>Skin &amp; Beauty</b>	▶ <b>Women's Health</b>	▶ <b>All Health Centers</b>
⊙ Allergic Asthma?	⊙ Alzheimer's Treatment	⊙ Bipolar Rx Info	⊙ Cancer Support Network	⊙ Epilepsy Assessment
⊙ Heart Failure Solutions	⊙ Living With Knee Pain	⊙ Nighttime GERD	⊙ Resistant Depression	⊙ Save on Your Rx

**A-Z Health Guides:** Conditions A-Z | Topics A-Z | Symptoms A-Z | Tests A-Z | Drugs A-Z | Tools A-Z | New! Videos A-Z

**Health Services:** Today's News | Find a Doctor | Symptom Checker | Health Care Services

**Subscription Services:** WebMD News via RSS | Newsletters | WebMD Weight Loss Clinic | WebMD Fertility Center | WebMD Health Manager

About WebMD | Terms of Use | Privacy Policy | Sponsor Policy | Site Map | Link to Us  
Contact Us | Emdeon™ | WebMD Corporate | Medscape® | MedicineNet® | RxList®

©2005-2006 WebMD, Inc. All rights reserved.

WebMD does not provide medical advice, diagnosis or treatment. See additional information.



Health On the Net Foundation

This is Google's cache of [http://en.wikipedia.org/wiki/Protein\\_kinase](http://en.wikipedia.org/wiki/Protein_kinase) as retrieved on Aug 24, 2006 17:19:27 GMT. Google's cache is the snapshot that we took of the page as we crawled the web. The page may have changed since that time. [Click here for the current page without highlighting.](#) This cached page may reference images which are no longer available. [Click here for the cached text only.](#) To link to or bookmark this page, use the following url: [http://www.google.com/search?q=cache:c07Lt\\_czGDUJ:en.wikipedia.org/wiki/Protein\\_kinase+protein+kinase+c+camp&hl=en&gl=us&ct=clnk&cd=1](http://www.google.com/search?q=cache:c07Lt_czGDUJ:en.wikipedia.org/wiki/Protein_kinase+protein+kinase+c+camp&hl=en&gl=us&ct=clnk&cd=1)

*Google is neither affiliated with the authors of this page nor responsible for its content.*

These search terms have been highlighted: **protein kinase c camp**

# Protein kinase

From Wikipedia, the free encyclopedia

A **protein kinase** is an enzyme that modifies other proteins by chemically adding phosphate groups to them (phosphorylation). This usually results in a functional change of the target **protein** (substrate) by changing enzyme activity, cellular location, or association with other proteins. Up to 30% of all proteins may be modified by **kinase** activity, and kinases are known to regulate the majority of cellular pathways, especially those involved in signal transduction, the transmission of signals within the cell. The human genome contains about 500 **protein kinase** genes; they constitute about 2% of all eukaryotic genes.

The chemical activity of a **kinase** involves removing a phosphate group from ATP and covalently attaching it to one of three amino acids that have a free hydroxyl group. Most kinases act on both serine and threonine, others act on tyrosine, and a number (dual specificity kinases) act on all three.

Because **protein** kinases have profound effects on a cell, their activity is highly regulated. Kinases are turned on or off by phosphorylation (sometimes by the **kinase** itself - *cis*-phosphorylation/autophosphorylation), by binding of activator proteins or inhibitor proteins, or small molecules, or by controlling their location in the cell relative to their substrates.

Disregulated **kinase** activity is a frequent cause of disease, particularly cancer, where kinases regulate many aspects that control cell growth, movement and death. Drugs which inhibit specific kinases are being developed to treat several diseases, and some are currently in clinical use, including Gleevec (imatinib) and Iressa (gefitinib).

## Contents

- 1 Serine/threonine-specific **protein** kinases
  - 1.1 Phosphorylase **kinase**
  - 1.2 **Protein kinase A**
    - 1.2.1 Regulation
  - 1.3 **Protein Kinase B**
  - 1.4 **Protein kinase C**
    - 1.4.1 Structure and regulation
    - 1.4.2 Function
  - 1.5 Ca<sup>2+</sup>/calmodulin-dependent **protein** kinases
    - 1.5.1 Structure and autoregulation
  - 1.6 MAP kinases
  - 1.7 Mos/Raf kinases
- 2 Tyrosine-specific **protein** kinases
  - 2.1 Receptor tyrosine kinases
    - 2.1.1 Structure
    - 2.1.2 Regulation
    - 2.1.3 Signal transduction
  - 2.2 Receptor-associated tyrosine kinases

- 3 Histidine-specific **protein** kinases
- 4 Aspartic acid/glutamic acid-specific **protein** kinases
- 5 Mixed kinases
- 6 External links

## Serine/threonine-specific protein kinases

Serine/threonine **protein** kinases (EC 2.7.11.1 (<http://www.expasy.org/cgi-bin/nicezyme.pl?2.7.11.1>)) phosphorylate the OH group of serine or threonine (which have similar sidechains). Activity of these **protein** kinases can be regulated by specific events (e.g. DNA damage), as well as numerous chemical signals, including:

- cAMP/cGMP
- Diacylglycerol
- Ca<sup>2+</sup>/calmodulin

While serine/threonine kinases all phosphorylate serine or threonine residues in their substrates, they select specific residues to phosphorylate on the basis of residues that flank the phosphoacceptor site, which together comprise the *consensus sequence*. Since the consensus sequence residues of the substrate to be phosphorylated make contact with the catalytic cleft of the kinase at several key amino acids (usually through hydrophobic forces and ionic bonds), a kinase is usually not specific to a single substrate, but instead can phosphorylate a whole "substrate family" having common recognition sequences. While the catalytic domain of these kinases is highly conserved, the sequence variation that is observed in the kinome (the subset of genes in the genome that encode kinases) provides for recognition of distinct substrates. Most kinases are inhibited by a pseudosubstrate that binds to the kinase like a real substrate but lacks the amino acid to be phosphorylated. When the pseudosubstrate is removed, the kinase can perform its normal function.

Many serine/threonine **protein** kinases do not have their own individual EC numbers and use "2.7.11.1". These were formerly included in EC number "2.7.1.37", which was a general EC number for any enzyme that phosphorylates proteins while converting ATP to ADP (i.e. ATP:**protein** phosphotransferases.) This category is currently being reviewed by the Nomenclature Committee of IUBMB (NC-IUBMB), and it is believed that the various serine/threonine-kinases will get their own EC numbers eventually.

Pelle is a serine/threonine kinase that can phosphorylate itself, and also Tube and Toll.

### Phosphorylase kinase

Phosphorylase kinase (EC 2.7.11.19 (<http://www.expasy.org/cgi-bin/nicezyme.pl?2.7.11.19>)) was in fact, the first Ser/Thr **protein** kinase to be discovered (in 1959 by Krebs *et al.*).

### Protein kinase A

**Protein kinase A** (EC 2.7.11.1 (<http://www.expasy.org/cgi-bin/nicezyme.pl?2.7.11.1>)) consists of two domains, a small domain with several  $\beta$  sheet structures and a larger domain containing several  $\alpha$  helices. The binding sites for substrate and ATP are located in the catalytic cleft between the domains (or lobes). When ATP and substrate bind, the two lobes rotate so that the terminal phosphate group of the ATP and the target amino acid of the substrate move into the correct positions for the catalytic reaction to take place.

### Regulation

**Protein kinase A** has several functions in the cell, including regulation of glycogen, sugar, and lipid metabolism. It is controlled by cAMP: in the absence of cAMP, the kinase is a tetramer of two regulatory and two catalytic subunits (R<sub>2</sub>C<sub>2</sub>), with the regulatory subunits blocking the catalytic center of the catalytic subunits. Binding of cAMP to the regulatory subunit leads to dissociation of active RC dimers. Also, the catalytic subunit itself can be regulated by phosphorylation.

Downregulation of **protein kinase A** occurs by a feedback mechanism: one of the substrates that is activated by the **kinase** is a phosphodiesterase, which converts **cAMP** to AMP, thus reducing the amount of **cAMP** that can activate **protein kinase A**.

## Protein Kinase B

**Protein Kinase B** is also known as **AKT kinase**. The v-akt gene was identified as the oncogene of retrovirus AKT8. The gene codes for a **protein kinase**. Human homologs of the AKT8 oncogenic **protein** were identified in 1987. By 1995 it had been found that Akt kinases function as mitogen-activated kinases downstream from cell surface receptors that activate phosphoinositide 3-kinase. Three human akt genes exist. All three Akt kinases regulate cell proliferation and Akt2 is particularly important for insulin actions in cells. A major target of Akt kinases is glycogen synthase **kinase-3**.

## Protein kinase C

**Protein kinase C** ('PKC', EC 2.7.11.1 (<http://www.expasy.org/cgi-bin/nicezyme.pl?2.7.11.1>)) is actually a family of **protein kinases** consisting of ~10 isozymes. They are divided into three subfamilies: conventional (or classical), novel, and atypical based on their second messenger requirements. Conventional (c)PKCs contain the isoforms  $\alpha$ ,  $\beta_1$ ,  $\beta_2$ , and  $\gamma$ . These require  $\text{Ca}^{2+}$ , diacylglycerol (DAG), and a phospholipid such as phosphatidylcholine for activation. Novel (n)PKCs include the  $\delta$ ,  $\epsilon$ ,  $\eta$ , and  $\theta$  isoforms, and require DAG, but do not require  $\text{Ca}^{2+}$  for activation. Thus, conventional and novel PKCs are activated through the same signal transduction pathway as phospholipase C. On the other hand, Atypical (a)PKCs (including  $\zeta$  and  $\iota/\lambda$  isoforms) require neither  $\text{Ca}^{2+}$  nor diacylglycerol for activation. The term "**protein kinase C**" usually refers to the entire family of isoforms.

### Structure and regulation

The structure of all PKCs consists of a regulatory domain and a catalytic domain tethered together by a hinge region. The catalytic region is highly homologous among the different isoforms, as well as to a lesser degree the catalytic region of other serine/threonine kinases. The second messenger requirement differences in the isoforms are a result of the regulatory region, which are similar within the classes, but differ among them. Most of the crystal structure of the catalytic region of PKC has not been determined, except for PKC theta and iota. Due to its similarity to other kinases whose crystal structure have been determined, the structure can be strongly predicted.

The regulatory domain or the amino-terminus of the PKCs contains several shared subregions. The C1 domain, present in all of the isoforms of PKC has a binding site for DAG as well as non-hydrolysable, non-physiological analogues called phorbol esters. This domain is functional and capable of binding DAG in both conventional and novel isoforms, however, the C1 domain in atypical PKCs is incapable of binding to DAG or phorbol esters. The C2 domain acts as a  $\text{Ca}^{2+}$  sensor and is present in both conventional and novel isoforms, but functional as a  $\text{Ca}^{2+}$  sensor only in the conventional. The pseudosubstrate region, which is present in all three classes of PKC, is a small sequence of amino acids that mimic a substrate and bind the substrate-binding cavity in the catalytic domain keeping the enzyme inactive. When  $\text{Ca}^{2+}$  and DAG are present in sufficient concentrations, they bind to the C2 and C1 domain, respectively, and recruit PKC to the membrane. This interaction with the membrane results in release of the pseudosubstrate from the catalytic site and activation of the enzyme. In order for these allosteric interactions to occur, however, PKC must first be properly folded and in the correct conformation permissive for catalytic action. This is contingent upon phosphorylation of the catalytic region, discussed below.

The catalytic region or **kinase core** of the PKA, PKB (also known as Akt) and PKC kinases contains approximately 40% amino acid sequence similarity. This similarity increases to ~70% across PKCs and even higher when comparing within classes. For example, the two atypical PKC isoforms,  $\zeta$  and  $\iota/\lambda$ , are 84% identical (Selbie et al., 1993). Of the over 30 **protein kinase** structures whose crystal structure has been revealed, all of them have the same basic organization. They are a bilobal structure with a  $\beta$  sheet comprising the N-terminal lobe and an  $\alpha$  helix constituting the C-terminal lobe. Both the ATP- and substrate-binding sites are located in the cleft formed by these two lobes. This is also where the pseudosubstrate domain of the regulatory region binds. Another feature of the PKC catalytic region that is essential to the viability of the **kinase** is its phosphorylation. The catalytic and novel PKCs have three phosphorylation sites, termed: the activation loop, the turn motif, and the hydrophobic motif. The atypical PKCs are phosphorylated only on the activation loop and the turn motif. Phosphorylation of the hydrophobic motif is rendered unnecessary by the presence of a glutamic acid in place of a serine, which, as a negative charge, acts similarly to a

phosphorylated residue. These phosphorylation events are essential for the activity of the enzyme, and 3-phosphoinositide-dependent **protein kinase-1** (PDK1) is the upstream kinase responsible for initiating the process by transphosphorylation of the activation loop. (Balendran et al., 2000)

Upon activation, **protein kinase C** enzymes are translocated to the plasma membrane by RACK proteins (membrane-bound receptor for activated **protein kinase C** proteins). The **protein kinase C** enzymes are known for their long-term activation: they remain activated after the original activation signal or the  $\text{Ca}^{2+}$ -wave is gone. This is presumably achieved by the production of diacylglycerol from phosphatidylcholine by a phospholipase; fatty acids may also play a role in long-term activation.

### Function

The consensus sequence of **protein kinase C** enzymes is similar to that of **protein kinase A**, since it contains basic amino acids close to the Ser/Thr to be phosphorylated. Their substrates are MARCKS proteins, MAP kinase, transcription factor inhibitor I $\kappa$ B, the vitamin D<sub>3</sub> receptor VDR, Raf kinase, calpain, and the epidermal growth factor receptor.

### $\text{Ca}^{2+}$ /calmodulin-dependent protein kinases

Also called *CaM kinases* (EC 2.7.11.17 (<http://www.expasy.org/cgi-bin/nicezyme.pl?2.7.11.17>)), these kinases are primarily regulated by the  $\text{Ca}^{2+}$ /calmodulin complex. These kinases show a memory effect on activation. Two types of CaM kinases are:

- *Specialized CaM kinases*. An example is the myosin light chain kinase (MLCK) that phosphorylates myosin, causing muscles to contract.
- *Multifunctional CaM kinases*. Also collectively called *CaM kinase II*, which play a role in many processes, such as neurotransmitter secretion, transcription factor regulation, and glycogen metabolism. Between 1% and 2% of the proteins in the brain are CaM kinase II.

### Structure and autoregulation

The CaM kinases consist of an N-terminal catalytic domain, a regulatory domain, and an association domain. In the absence of  $\text{Ca}^{2+}$ /calmodulin, the catalytic domain is autoinhibited by the regulatory domain, which contains a pseudosubstrate sequence. Several CaM kinases aggregate into a homooligomer or heterooligomer. Upon activation by  $\text{Ca}^{2+}$ /calmodulin, the activated CaM kinases autophosphorylate each other in an intermolecular reaction. This has two effects:

1. An increase in affinity for the calmodulin complex, prolonging the time the kinase is active.
2. Continued activation of the phosphorylated kinase complex even after the calmodulin complex has dissociated from the kinase complex, which prolongs the active state even more.

### MAP kinases

Mitogen-activated protein kinases (MAPKs) (EC 2.7.11.1) respond to extracellular stimuli (mitogens) and regulate various cellular activities, such as gene expression, mitosis, differentiation, and cell survival/apoptosis. Extracellular stimuli lead to activation of a MAPK via a signaling cascade composed of MAPK, MAPK kinase (MAPKK), and MAPKK kinase (MAPKKK). A MAPKKK that is activated by extracellular stimuli phosphorylates a MAPKK on its serine and threonine residues, and then this MAPKK activates a MAPK through phosphorylation on its serine and tyrosine residues. This MAPK signaling cascade has been evolutionarily well-conserved from yeast to mammals.

To date, four distinct groups of MAPKs have been characterized in mammals: (1) extracellular signal-regulated kinases (ERKs), (2) c-Jun N-terminal kinases (JNKs), (3) p38 isoforms, and (4) ERK5. The ERKs (also known as classical MAPKs) signaling pathway is preferentially activated in response to growth factors and phorbol ester (a tumor promoter), and regulates cell proliferation and cell differentiation. The JNKs (also known as stress-activated protein kinases; SAPKs) and p38 signaling pathways are responsive to stress stimuli, such as cytokines, ultraviolet irradiation, heat shock, and osmotic shock, and are involved in cell differentiation and apoptosis. And ERK5, which has been found recently, is activated both by growth factors and by stress stimuli, and it participates in cell proliferation.

## Mos/Raf kinases

Mos/Raf kinases form part of the MAPKK **Kinase** family and are activated by growth factors. The enzyme functions to stimulate growth of cells. Raf inhibition has become the target for new anti-metastatic cancer drugs as they inhibit the MAPK cascade and reduce cell proliferation.

## Tyrosine-specific protein kinases

*Main article: Tyrosine kinase*

Tyrosine-specific **protein kinases** (EC 2.7.10.1 (<http://www.expasy.org/cgi-bin/nicezyme.pl?2.7.10.1>)) phosphorylate tyrosine amino acid residues, and are, like serine/threonine-specific kinases, used in signal transduction. They act primarily as growth factor receptors and in downstream signaling from growth factors; some examples:

- Platelet-derived growth factor (PDGF) receptor;
- Epidermal growth factor (EGF) receptor;
- Insulin receptor and insulin-like growth factor (IGF1) receptor;
- Stem cell factor (*scf*) receptor (also called *c-kit*, see the article on gastrointestinal stromal tumor).

## Receptor tyrosine kinases

These kinases consist of a transmembrane receptor with a tyrosine **kinase** domain protruding into the cytoplasm. They play an important role in regulating cell division, cellular differentiation, and morphogenesis. More than 50 receptor tyrosine kinases are known in mammals.

### Structure

The extracellular domain serves as the ligand-binding part of the molecule. It can be a separate unit that is attached to the rest of the receptor by a disulfide bond. The same mechanism can be used to bind two receptors together to form a homo- or heterodimer. The transmembrane element is a single  $\alpha$  helix. The intracellular or cytoplasmic domain is responsible for the (highly conserved) **kinase** activity, as well as several regulatory functions.

### Regulation

Ligand binding causes two reactions:

1. Dimerization of two monomeric receptor kinases or stabilization of a loose dimer. Many ligands of receptor tyrosine kinases are multivalent. Some tyrosine receptor kinases (e.g., the platelet-derived growth factor receptor) can form heterodimers with other similar but not identical kinases of the same subfamily, allowing a highly varied response to the extracellular signal.
2. *Trans*-autophosphorylation (phosphorylation by the other **kinase** in the dimer) of the **kinase**.

The autophosphorylation causes the two subdomains of the intrinsic **kinase** to shift, opening the **kinase** domain for ATP binding. In the inactive form, the **kinase** subdomains are aligned so that ATP cannot reach the catalytic center of the **kinase**. When several amino acids suitable for phosphorylation are present in the **kinase** domain (e.g., the insulin-like growth factor receptor), the activity of the **kinase** can increase with the number of phosphorylated amino acids; in this case, the first phosphorylation is said to be a *cis*-autophosphorylation, switching the **kinase** from "off" to "standby".

### Signal transduction

The active tyrosine **kinase** phosphorylates specific target proteins, which are often enzymes themselves. An important target is the **ras protein** signal-transduction chain.

## Receptor-associated tyrosine kinases

Tyrosine kinases recruited to a receptor following hormone binding are receptor-associated tyrosine kinases and are involved in a number of signalling cascades, principally those involved in cytokine signalling (but also others, including growth hormone). One such receptor-associated tyrosine kinase is Janus kinase (JAK), many of whose effects are mediated by STAT proteins. (*See JAK-STAT pathway.*)

## Histidine-specific protein kinases

Histidine kinases are structurally distinct from most other protein kinases and are found mostly in prokaryotes as part of two-component signal transduction mechanisms. A phosphate group from ATP is first added to a histidine residue within the kinase, and later transferred to an aspartate residue on a 'receiver domain' on a different protein, or sometimes on the kinase itself. The aspartyl phosphate residue is then active in signaling.

Histidine kinases are found widely in prokaryotes, as well as in plants and fungi. The pyruvate dehydrogenase family of kinases in animals is structurally related to histidine kinases, but instead phosphorylate serine residues, and probably do not use a phospho-histidine intermediate.

## Aspartic acid/glutamic acid-specific protein kinases

## Mixed kinases

Some kinases have mixed kinase activities. For example, MEK (MAPKK), which is involved in the MAP kinase cascade, is a mixed serine/threonine and tyrosine kinase.

## External links

- The Protein Kinase Resource (<http://pkr.sdsc.edu/>): Curated database of protein kinase structures and related data
- Protein kinase gene resource (<http://www.kinase.com/>): Genomic analyses, classification and evolution of protein kinases
- Kinase3D: A Database of Protein Kinase 3D models provided by GEN2X.com (<http://www.gen2x.com/news.html>)
- Collection of Ser/Thr/Tyr specific protein kinases and similar sequences (<http://hodgkin.mbu.iisc.ernet.in/~king/>)
- KinMutBase: A registry of disease-causing mutations in protein kinase domains (<http://bioinf.uta.fi/KinMutBase/>)
- Evolution of protein kinase signaling from yeast to man ([http://kinase.com/evolution/TiBS\\_Kinase\\_Evolution.pdf](http://kinase.com/evolution/TiBS_Kinase_Evolution.pdf)) (pdf)

### Cell signaling

**Key concepts** - Ligand | Receptor | Second messenger | **Protein kinase** | Transcription factor | Cell signaling networks

**Pathways** - Apoptosis | Ca<sup>2+</sup> signaling | Cytokine signaling | Hedgehog | Integrin signaling | JAK/STAT | Lipid signaling | MAPK/ERK pathway | mTOR | NF-κB | Notch | p53 | TGFβ | Wnt


Retrieved from "http://en.wikipedia.org/wiki/Protein\_kinase"

Categories: Articles with sections needing expansion | EC 2.7 | Protein kinases

- This page was last modified 22:14, 13 August 2006.
  - All text is available under the terms of the GNU Free Documentation License. (See **Copyrights** for details.)
- Wikipedia® is a registered trademark of the Wikimedia Foundation, Inc.

1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L2 ANSWER 35 OF 35 REGISTRY COPYRIGHT 2006 ACS on STN  
RN 21829-25-4 REGISTRY  
ED Entered STN: 16 Nov 1984  
CN 3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-  
dimethyl ester (9CI) (CA INDEX NAME)  
OTHER CA INDEX NAMES:  
CN 3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(o-nitrophenyl)-  
dimethyl ester (8CI)  
OTHER NAMES:  
CN 2,6-Dimethyl-3,5-dicarbomethoxy-4-(2-nitrophenyl)-1,4-dihydropyridine  
CN 2,6-Dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid  
dimethyl ester  
CN 4-(2-Nitrophenyl)-2,6-dimethyl-3,5-dicarbomethoxy-1,4-dihydropyridine  
CN Adalat  
CN Adalat 10  
CN Adalat 20  
CN Adalat 5  
CN Adalat CC  
CN Adalat CR  
CN Adalat Crono  
CN Adalat FT  
CN Adalat GITS  
CN Adalat GITS 30  
CN Adalat LA  
CN Adalat LP  
CN Adalat Oros  
CN Adalat PA  
CN Adalat retard  
CN Adalate  
CN Adapine  
CN Adapress  
CN Alat  
CN Aldipin  
CN Alfadat  
CN Alonix  
CN Alonix S  
CN **Alpha-Nifedipine Retard**  
CN Angipece  
CN Anifed  
CN Anpine  
CN Apo-Nifed  
CN Aprical  
CN BAY 1040  
CN BAY-a 1040  
CN Bonacid  
CN Calcibloc  
CN Calcigard  
CN Calcilat  
CN Camont  
CN Cardifen  
CN Cardilat  
CN Cardilate  
CN Cardionorm  
CN Chronadalate  
CN Chronadalate LP  
CN Citilat  
CN Coracten  
CN Coral  
CN Cordafen  
CN **Nifedipine**  
CN **Nifedipine retard**



ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for  
DISPLAY

FS 3D CONCORD

DR 11104-22-6, 101539-70-2, 101554-38-5

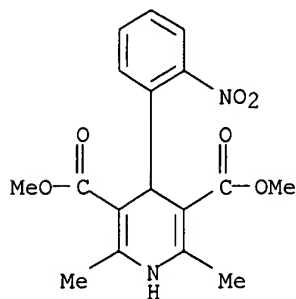
MF C17 H18 N2 O6

CI COM

LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN\*, BIOSIS,  
BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMINFORMRX, CHEMLIST,  
CIN, CSCHEM, CSNB, DDFU, DETHERM\*, DRUGU, EMBASE, IFICDB, IFIPAT,  
IFIUDB, IMSCOSEARCH, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE,  
MRCK\*, MSDS-OHS, PATDPASPC, PHAR, PROMT, PROUSDDR, PS, RTECS\*,  
SCISEARCH, SPECINFO, TOXCENTER, USAN, USPAT2, USPATFULL, VETU  
(\*File contains numerically searchable property data)

Other Sources: DSL\*\*, EINECS\*\*, WHO

(\*\*Enter CHEMLIST File for up-to-date regulatory information)



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

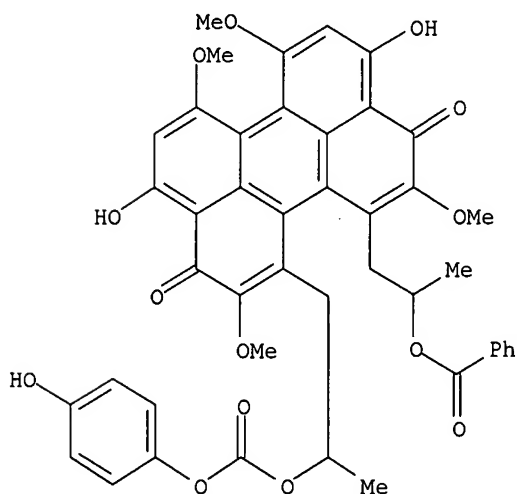
7847 REFERENCES IN FILE CA (1907 TO DATE)

106 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

7861 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=>

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2006 ACS on STN  
 RN 121263-19-2 REGISTRY  
 ED Entered STN: 23 Jun 1989  
 CN Carbonic acid, (1R)-2-[12-[(2R)-2-(benzoyloxy)propyl]-3,10-dihydro-4,9-dihydroxy-2,6,7,11-tetramethoxy-3,10-dioxo-1-perylenyl]-1-methylethyl 4-hydroxyphenyl ester, stereoisomer (9CI) (CA INDEX NAME)  
 OTHER CA INDEX NAMES:  
 CN Perylene, carbonic acid deriv.  
 OTHER NAMES:  
 CN **Calphostin C**  
 CN Cladochrome E  
 CN PKF 115-584  
 CN UCN 1028C  
 DR 125411-36-1  
 MF C44 H38 O14  
 SR CA  
 LC STN Files: ADISINSIGHT, AGRICOLA, ANABSTR, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CHEMCATS, CSCHM, DDFU, DRUGU, EMBASE, IMSDRUGNEWS, IMSRESEARCH, IPA, MEDLINE, NAPRALERT, PHAR, PROMT, RTECS\*, TOXCENTER, USPAT2, USPATFULL  
 (\*File contains numerically searchable property data)



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

274 REFERENCES IN FILE CA (1907 TO DATE)  
 2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA  
 274 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> d 12 30-35

L5 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2006 ACS on STN

RN 21829-25-4 REGISTRY

ED Entered STN: 16 Nov 1984

CN 3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-  
, dimethyl ester (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(o-nitrophenyl)-  
, dimethyl ester (8CI)

OTHER NAMES:

CN 2,6-Dimethyl-3,5-dicarbomethoxy-4-(2-nitrophenyl)-1,4-dihydropyridine

CN 2,6-Dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid  
dimethyl ester

CN 4-(2-Nitrophenyl)-2,6-dimethyl-3,5-dicarbomethoxy-1,4-dihydropyridine

CN Adalat

CN Adalat 10

CN Adalat 20

CN Adalat 5

CN Adalat CC

CN Adalat CR

CN Adalat Crono

CN Adalat FT

CN Adalat GITS

CN Adalat GITS 30

CN Adalat LA

CN Adalat LP

CN Adalat Oros

CN Adalat PA

CN Adalat retard

CN Adalate

CN Adapine

CN Adapress

CN Alat

CN Aldipin

CN Alfadat

CN Alonix

CN Alonix S

CN Alpha-Nifedipine Retard

CN Angipec

CN Anifed

CN Anpine

CN Apo-Nifed

CN Aprical

CN BAY 1040

CN BAY-a 1040

CN Bonacid

CN Calcibloc

CN Calcigard

CN Calcilat

CN Camont

CN Cardifen

CN Cardilat

CN Cardilate

CN Cardionorm

CN Chronadalate

CN Chronadalate LP

CN Citilat

CN Coracten

CN Coral

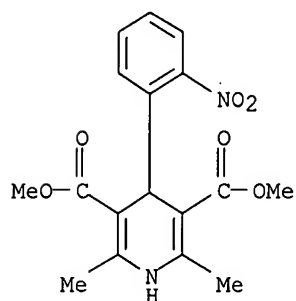
CN Cordafen

CN Procardia

CN Procardia XL

ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for

DISPLAY  
 FS 3D CONCORD  
 DR 11104-22-6, 101539-70-2, 101554-38-5  
 MF C17 H18 N2 O6  
 CI COM  
 LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN\*, BIOSIS,  
 BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMINFORMRX, CHEMLIST,  
 CIN, CSChem, CSNB, DDFU, DETHERM\*, DRUGU, EMBASE, IFICDB, IFIPAT,  
 IFIUDB, IMSCoSEARCH, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE,  
 MRCK\*, MSDS-OHS, PATDPASPC, PHAR, PROMT, PROUSDDR, PS, RTECS\*,  
 SCISEARCH, SPECINFO, TOXCENTER, USAN, USPAT2, USPATFULL, VETU  
 (\*File contains numerically searchable property data)  
 Other Sources: DSL\*\*, EINECS\*\*, WHO  
 (\*\*Enter CHEMLIST File for up-to-date regulatory information)



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

7847 REFERENCES IN FILE CA (1907 TO DATE)  
 106 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA  
 7861 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=>

=> d ibib abs 1-8 it hitstr

L11 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:49003 CAPLUS

DOCUMENT NUMBER: 142:329754

TITLE: **Nifedipine** protects against overproduction of superoxide anion by monocytes from patients with systemic sclerosis

AUTHOR(S): Allanore, Yannick; Borderie, Didier; Perianin, Axel; Lemarechal, Herve; Ekindjian, Ohvanesse Garabed; Kahan, Andre

CORPORATE SOURCE: Rheumatology A Department, Assistance Publique-Hopitaux de Paris, Paris V University, Cochin Hospital, Paris, Fr.

SOURCE: Arthritis Research & Therapy (2005), 7(1), R93-R100  
CODEN: ARTRCV; ISSN: 1478-6362  
URL: <http://arthritis-research.com/content/pdf/ar1457.pdf>

PUBLISHER: BioMed Central Ltd.

DOCUMENT TYPE: Journal; (online computer file)

LANGUAGE: English

AB We have reported previously that dihydropyridine-type calcium-channel antagonists (DTCCA) such as **nifedipine** decrease plasma markers of oxidative stress damage in systemic sclerosis (SSc). To clarify the cellular basis of these beneficial effects, we investigated the effects in vivo and in vitro of **nifedipine** on superoxide anion (O<sub>2</sub><sup>•-</sup>) production by peripheral blood monocytes. We compared 10 healthy controls with 12 patients with SSc, first after interruption of treatment with DTCCA and second after 2 wk of treatment with **nifedipine** (60 mg/day). O<sub>2</sub><sup>•-</sup> production by monocytes stimulated with phorbol myristate acetate (PMA) was quantified by the cytochrome c reduction method. We also investigated the effects in vitro of DTCCA on O<sub>2</sub><sup>•-</sup> production and protein phosphorylation in healthy monocytes and on protein kinase C (PKC) activity using recombinant PKC. After DTCCA had been washed out, monocytes from patients with SSc produced more O<sub>2</sub><sup>•-</sup> than those from controls. **Nifedipine** treatment considerably decreased O<sub>2</sub><sup>•-</sup> production by PMA-stimulated monocytes. Treatment of healthy monocytes with **nifedipine** in vitro inhibited PMA-induced O<sub>2</sub><sup>•-</sup> production and protein phosphorylation in a dose-dependent manner. Finally, **nifedipine** strongly inhibited the activity of recombinant PKC in vitro. Thus, the oxidative stress damage observed in SSc is consistent with O<sub>2</sub><sup>•-</sup> overprod. by primed monocytes. This was decreased by **nifedipine** treatment both in vivo and in vitro. This beneficial property of **nifedipine** seems to be mediated by its cellular action and by the inhibition of PKC activity. This supports the hypothesis that this drug could be useful for the treatment of diseases associated with oxidative stress.

IT Respiration, animal  
(burst; **nifedipine** dose dependently inhibited fMLP-induced monocyte respiratory burst in systemic sclerosis patients)

IT Calcium channel blockers  
Human

(dihydropyridine-type calcium-channel antagonist **nifedipine** inhibited PKC and PMA induced over production of super oxide anion and protein phosphorylation in peripheral blood monocytes of systemic sclerosis patients)

IT Antioxidants  
(**nifedipine** had anti-oxidant effect by inhibiting PKC and PMA induced over production of super oxide anion in peripheral blood monocytes of systemic sclerosis patients)

IT Connective tissue, disease  
(**nifedipine** inhibited PKC and PMA induced over production of super oxide anion in peripheral blood monocytes of patients with

systemic sclerosis)

IT Monocyte  
(**nifedipine** inhibited PKC and PMA induced over production of super oxide anion in peripheral blood monocytes of systemic sclerosis patients)

IT Connective tissue, disease  
(scleroderma; **nifedipine** inhibited PKC and PMA induced over production of super oxide anion in peripheral blood monocytes of patients with systemic sclerosis)

IT 55985-32-5, Nicardipine  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(calcium channel blockers **nifedipine** and nicardipine had similar inhibitory effect on superoxide anion production from monocytes of healthy humans)

IT 121263-19-2, Calphostin C 133052-90-1, GF109203x  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(dihydropyridine-type calcium-channel antagonist **nifedipine** inhibited PKC and PMA induced over production of super oxide anion and protein phosphorylation in peripheral blood monocytes of systemic sclerosis patients)

IT 21829-25-4, **Nifedipine**  
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(dihydropyridine-type calcium-channel antagonist **nifedipine** inhibited PKC and PMA induced over production of super oxide anion and protein phosphorylation in peripheral blood monocytes of systemic sclerosis patients)

IT 7722-84-1, Hydrogen peroxide, biological studies  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(**nifedipine** dose dependently inhibited fMLP-induced hydrogen peroxide production from healthy monocytes)

IT 11062-77-4, Superoxide anion  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(**nifedipine** dose dependently inhibited phorbol myristate acetate-induced monocyte superoxide anion production in systemic sclerosis patients and healthy humans)

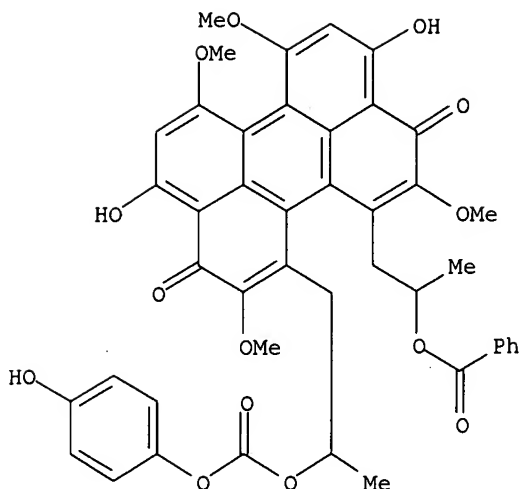
IT 141436-78-4, Protein kinase C  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(**nifedipine** dose dependently inhibited protein kinase C-dependent monocyte protein phosphorylation in vitro and in vivo from patient with systemic sclerosis)

IT 42399-41-7, Diltiazem  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(**nifedipine** had high inhibitory effect on superoxide anion production from monocytes of healthy humans than calcium channel blocker diltiazem)

IT 121263-19-2, Calphostin C  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(dihydropyridine-type calcium-channel antagonist **nifedipine** inhibited PKC and PMA induced over production of super oxide anion and protein phosphorylation in peripheral blood monocytes of systemic sclerosis patients)

RN 121263-19-2 CAPLUS

CN Carbonic acid, (1R)-2-[12-[(2R)-2-(benzoyloxy)propyl]-3,10-dihydro-4,9-dihydroxy-2,6,7,11-tetramethoxy-3,10-dioxo-1-perylenyl]-1-methylethyl 4-hydroxyphenyl ester, stereoisomer (9CI) (CA INDEX NAME)



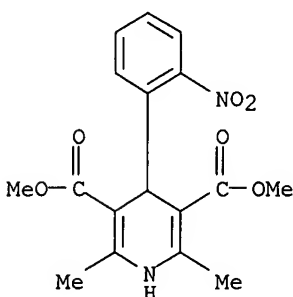
IT 21829-25-4, Nifedipine

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(dihydropyridine-type calcium-channel antagonist **nifedipine** inhibited PKC and PMA induced over production of super oxide anion and protein phosphorylation in peripheral blood monocytes of systemic sclerosis patients)

RN 21829-25-4 CAPLUS

CN 3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2006:157149 CAPLUS

DOCUMENT NUMBER: 145:180830

TITLE: Effects of emodin on Ca<sup>2+</sup> signal transduction of smooth muscle cells in multiple organ dysfunction syndrome

AUTHOR(S): Chen, Zheyu; Qinghui, Q. I.; Liu, Lixin; Tao, M. A.; Xu, Jian; Zhang, Liang; Yan, Lunan

CORPORATE SOURCE: Department of General Surgery of West China Hospital, Sichuan University, Chengdu, Peop. Rep. China

SOURCE: Journal of Surgical Research (2006), 131(1), 80-85  
CODEN: JSGRA2; ISSN: 0022-4804

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We have made several reports on the signal transduction mechanism that emodin enhance the calcium concns. of smooth muscle cells (SMCs) in the physiol. condition by inositol [1,4,5]-triphosphate (IP3). The observation that IP3 concns. in SMCs were decreased in multiple organ dysfunction syndrome (MODS) prompted us to ask whether emodin can activate SMCs to contract by way of elevating  $[Ca^{2+}]$  and thus modulating the critical  $Ca^{2+}$  signal transduction pathways involved in the contraction of the SMCs in the pathol. setting of MODS. To test this hypothesis, we used the rat model of MODS to explore the potential roles of emodin in  $Ca^{2+}$  signal transduction in the SMCs of colon in rats. ML-7 [an inhibitor of myosin light-chain kinase (MLCK)] and Calphostin C [an inhibitor of protein kinase C (PKC)] were used to observe the influence of emodin on the muscle strips and SMCs in rats after MODS. Nifedipine (an antagonist of voltage-gated  $Ca^{2+}$  channel), EGTA (removal of extracellular  $Ca^{2+}$ ), heparin (a specific IP3 receptor antagonist), and ryanodine were used to probe the potential mechanisms involved in emodin-mediated elevation of the global cytoplasmic  $Ca^{2+}$  in SMCs of colon in the rats after MODS. Our results show that emodin is capable of contract the smooth muscles of colon in rats after MODS by MLCK increasing  $[Ca^{2+}]$  of SMCs, and by PKC enhancing the calcium sensitivity of SMCs. The mechanism by which emodin triggers elevated  $[Ca^{2+}]$  of smooth muscles of colon in rats after MODS is likely to operate through IP3 and RyR receptors in the sarcoplasm. It is hoped that deeper insights into how emodin modulates the critical calcium signaling in SMCs might lead to the potential development of emodin in the treatment of MODS.

IT Intestine  
(colon; emodin induced colonic smooth muscle contraction by signal path of MLCK increasing  $[Ca^{2+}]$  through IP3 and RyR receptors in sarcoplasm and by PKC path enhancing calcium sensitivity in SMCs of multiple organ dysfunction syndrome rat model)

IT Signal transduction, biological  
(emodin contracted colonic smooth muscle by both signal path of MLCK increasing  $[Ca^{2+}]$  through IP3 and RyR receptors in sarcoplasm and PKC path enhancing calcium sensitivity in multiple organ dysfunction syndrome rat model)

IT Multiple organ failure  
Muscle contraction  
(emodin induced colonic smooth muscle contraction by signal path of MLCK increasing  $[Ca^{2+}]$  through IP3 and RyR receptors in sarcoplasm and by PKC path enhancing calcium sensitivity in SMCs of multiple organ dysfunction syndrome rat model)

IT Ryanodine receptors  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(emodin induced colonic smooth muscle contraction by signal path of myosin light-chain kinase increasing  $[Ca^{2+}]$  through RyR receptor in sarcoplasm of multiple organ dysfunction syndrome rat model)

IT Inositol 1,4,5-trisphosphate receptors  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(emodin induced colonic smooth muscle contraction by signal path of myosin light-chain kinase increasing  $[Ca^{2+}]$  through inositol [1, 4, 5]-triphosphate receptor in sarcoplasm of multiple organ dysfunction syndrome rat model)

IT Rheum palmatum  
(emodin isolated from Rheum palmatum contracted colonic smooth muscle by MLCK path elevating  $[Ca^{2+}]$  via IP3 and RyR receptor in sarcoplasm, by PKC path enhancing calcium sensitivity in SMC of multiple organ dysfunction syndrome rat model)

IT Muscle  
(smooth; emodin induced colonic smooth muscle contraction by signal path of MLCK increasing  $[Ca^{2+}]$  through IP3 and RyR receptors in sarcoplasm and by PKC path enhancing calcium sensitivity in SMCs of multiple organ dysfunction syndrome rat model)

IT 518-82-1, Emodin

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (anthraquinone derivative emodin contracted colonic smooth muscle by MLCK path increasing [Ca<sup>2+</sup>] via IP<sub>3</sub> and RyR receptor in sarcoplasm and by PKC path enhancing calcium sensitivity in SMC of multiple organ dysfunction syndrome rat model)

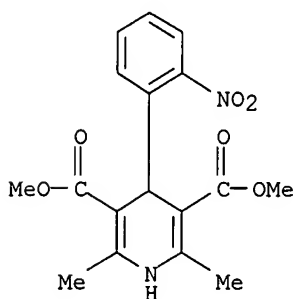
IT 14127-61-8, Calcium ion, biological studies  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (emodin induced colonic smooth muscle contraction by signal path of MLCK increasing [Ca<sup>2+</sup>] through IP<sub>3</sub> and RyR receptors in sarcoplasm and by PKC path enhancing calcium sensitivity in SMCs of multiple organ dysfunction syndrome rat model)

IT 109376-83-2, ML-7  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (emodin induced colonic smooth muscle contraction by signal path of myosin light-chain kinase increasing [Ca<sup>2+</sup>] through inositol [1, 4, 5]-triphosphate and RyR receptors in sarcoplasm of multiple organ dysfunction syndrome rat model)

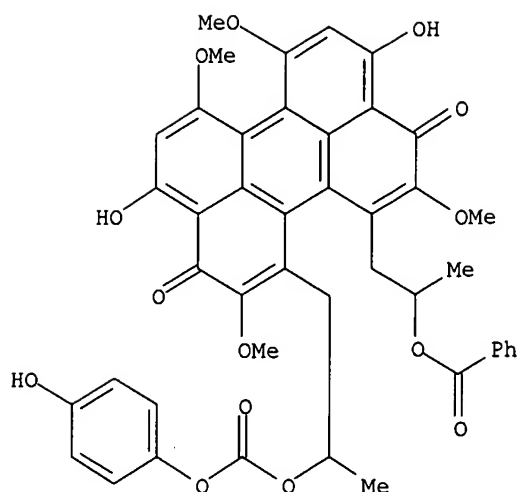
IT 67-42-5, EGTA 9005-49-6, Heparin, biological studies 15662-33-6, Ryanodine **21829-25-4, Nifedipine 121263-19-2**, Calphostin c  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (emodin induced colonic smooth muscle contraction by signal path of protein kinase C enhancing calcium sensitivity in smooth muscle cells of multiple organ dysfunction syndrome rat model)

IT **21829-25-4, Nifedipine 121263-19-2**, Calphostin c  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (emodin induced colonic smooth muscle contraction by signal path of protein kinase C enhancing calcium sensitivity in smooth muscle cells of multiple organ dysfunction syndrome rat model)

RN 21829-25-4 CAPLUS  
 CN 3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester (9CI) (CA INDEX NAME)



RN 121263-19-2 CAPLUS  
 CN Carbonic acid, (1R)-2-[12-[(2R)-2-(benzoyloxy)propyl]-3,10-dihydro-4,9-dihydroxy-2,6,7,11-tetramethoxy-3,10-dioxo-1-perylenyl]-1-methylethyl 4-hydroxyphenyl ester, stereoisomer (9CI) (CA INDEX NAME)



REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN  
 ACCESSION NUMBER: 2000:434972 CAPLUS  
 DOCUMENT NUMBER: 133:172003  
 TITLE: Effects of phorbol 12,13-diacetate on human isolated bronchus  
 AUTHOR(S): Sarria, B.; Pedros, C.; Galan, G.; Cortijo, J.; Morcillo, E. J.  
 CORPORATE SOURCE: Faculty of Medicine, Department of Pharmacology, University of Valencia, Valencia, E-46010, Spain  
 SOURCE: European Journal of Pharmacology (2000), 399(1), 65-73  
 CODEN: EJPHAZ; ISSN: 0014-2999  
 PUBLISHER: Elsevier Science B.V.  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

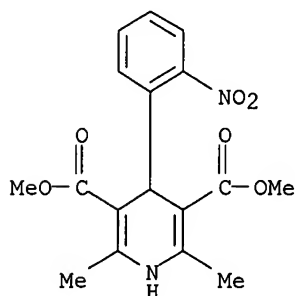
AB Protein kinase C appears to be involved in the regulation of airway contractility. Phorbol 12,13-diacetate (PDA; 0.01-10  $\mu$ M), a protein kinase C activator, produced a transient relaxation followed by a sustained contraction of human isolated bronchus. Different protein kinase C inhibitors (calphostin C, staurosporine and 1-(5-isoquinolinesulfonyl)-2-methylpiperazine) (H-7), **nifedipine** (NIF; 1  $\mu$ M) or incubation with  $\text{Ca}^{2+}$ -free medium, inhibited the spasmogenic response to phorbol, while ouabain (10  $\mu$ M) suppressed only the initial relaxation. These results indicate that the initial relaxation, in response to PDA, is related to the activation of  $\text{Na}^+/\text{K}^+$ -ATPase, while the ensuing contraction depends on extracellular  $\text{Ca}^{2+}$  entry. Incubation with PDA (1-5  $\mu$ M) depressed the maximal relaxation to theophylline and caffeine obtained at 37° but augmented the spasmogenic responses to methylxanthines (10 mM) obtained in cooled preps. These effects do not result apparently from increased extracellular entry of  $\text{Ca}^{2+}$ , but instead, from facilitation of the release of  $\text{Ca}^{2+}$  from intracellular stores.

IT Antiasthmatics  
 Bronchodilators

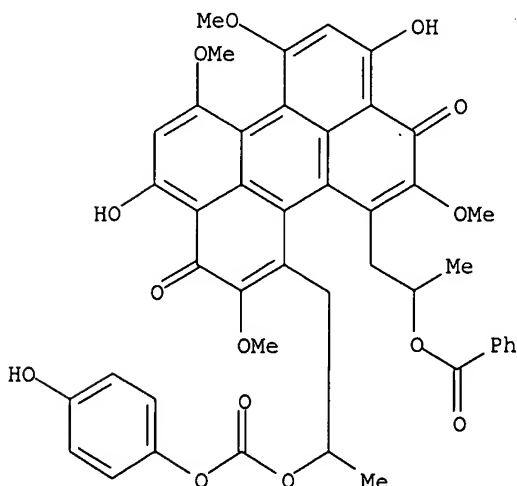
(effects of phorbol 12,13-diacetate on human isolated bronchus)  
 IT 58-08-2, Caffeine, biological studies 58-55-9, Theophylline, biological studies 7683-59-2, Isoprenaline 21829-25-4, **Nifedipine** 62996-74-1, Staurosporine 84477-87-2 94535-50-9, Levchromakalim 121263-19-2, Calphostin C

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES

(Uses)  
 (effects of phorbol 12,13-diacetate on human isolated bronchus)  
 IT 141436-78-4, Protein kinase C  
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
 (effects of phorbol 12,13-diacetate on human isolated bronchus)  
 IT 9000-83-3, ATPase  
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
 (potassium-sodium-activated; effects of phorbol 12,13-diacetate on human isolated bronchus)  
 IT 21829-25-4, Nifedipine 121263-19-2, Calphostin C  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (effects of phorbol 12,13-diacetate on human isolated bronchus)  
 RN 21829-25-4 CAPLUS  
 CN 3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester (9CI) (CA INDEX NAME)



RN 121263-19-2 CAPLUS  
 CN Carbonic acid, (1R)-2-[12-[(2R)-2-(benzoyloxy)propyl]-3,10-dihydro-4,9-dihydroxy-2,6,7,11-tetramethoxy-3,10-dioxo-1-perylenyl]-1-methylethyl 4-hydroxyphenyl ester, stereoisomer (9CI) (CA INDEX NAME)



REFERENCE COUNT:

42

THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2006:100738 CAPLUS

DOCUMENT NUMBER: 144:198849

TITLE: Novel dosage form comprising modified-release and immediate-release active ingredients

INVENTOR(S): Vaya, Navin; Karan, Rajesh Singh; Sadanand, Sunil; Gupta, Vinod Kumar

PATENT ASSIGNEE(S): India

SOURCE: U.S. Pat. Appl. Publ., 49 pp., Cont.-in-part of U.S. Ser. No. 630,446.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2006024365	A1	20060202	US 2005-134633	20050519
IN 193042	A	20040626	IN 2002-MU697	20020805
US 2004096499	A1	20040520	US 2003-630446	20030729
PRIORITY APPLN. INFO.:			IN 2002-MU697	A 20020805
			IN 2002-MU699	A 20020805
			IN 2003-MU80	A 20030122
			IN 2003-MU82	A 20030122
			US 2003-630446	A2 20030729

AB A dosage form comprising of a high dose, high solubility active ingredient as modified release and a low dose active ingredient as immediate release where the weight ratio of immediate release active ingredient and modified release active ingredient is from 1:10 to 1:15000 and the weight of modified release active ingredient per unit is from 500 mg to 1500 mg; a process for preparing the dosage form. Tablets containing 10 mg sodium pravastatin and 1000 mg niacin were prepared. The release of sodium pravastatin after 24 h was 67.7%, and the release of niacin after 1 h was 84.1%.

IT tRNA

L11 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:373373 CAPLUS  
DOCUMENT NUMBER: 141:99005  
TITLE: Prediction of P-Glycoprotein Substrates by a Support Vector Machine Approach  
AUTHOR(S): Xue, Y.; Yap, C. W.; Sun, L. Z.; Cao, Z. W.; Wang, J. F.; Chen, Y. Z.  
CORPORATE SOURCE: Department of Computational Science, Singapore-MIT Alliance, National University of Singapore, 117543, Singapore  
SOURCE: Journal of Chemical Information and Computer Sciences (2004), 44(4), 1497-1505  
CODEN: JCISD8; ISSN: 0095-2338  
PUBLISHER: American Chemical Society  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB P-glycoproteins (P-gp) actively transport a wide variety of chems. out of cells and function as drug efflux pumps that mediate multidrug resistance and limit the efficacy of many drugs. Methods for facilitating early elimination of potential P-gp substrates are useful for facilitating new drug discovery. A computational ensemble pharmacophore model has recently been used for the prediction of P-gp substrates with a promising accuracy of 63%. It is desirable to extend the prediction range beyond compds. covered by the known pharmacophore models. For such a purpose, a machine learning method, support vector machine (SVM), was explored for the prediction of P-gp substrates. A set of 201 chemical compds., including 116 substrates and 85 nonsubstrates of P-gp, was used to train and test a SVM classification system. This SVM system gave a prediction accuracy of at least 81.2% for P-gp substrates based on two different evaluation methods, which is substantially improved against that obtained from the multiple-pharmacophore model. The prediction accuracy for nonsubstrates of P-gp is 79.2% using 5-fold cross-validation. These accuracies are slightly better than those obtained from other statistical classification methods, including k-nearest neighbor (k-NN), probabilistic neural networks (PNN), and C4.5 decision tree, that use the same sets of data and mol. descriptors. The study indicates the potential of SVM in facilitating the prediction of P-gp substrates.

IT Biological transport  
Molecular modeling  
Multidrug resistance  
Pharmacophores  
Simulation and Modeling  
(prediction of P-glycoprotein substrates by support vector machine approach)

IT P-glycoproteins  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(prediction of P-glycoprotein substrates by support vector machine approach)

IT 50-02-2, Dexamethasone 50-06-6, Phenobarbital, biological studies  
50-07-7, Mitomycin-C 50-18-0, Cyclophosphamide 50-22-6, Corticosterone  
50-23-7, Hydrocortisone 50-24-8, Prednisolone 50-27-1, Estriol  
50-28-2, Estradiol, biological studies 50-52-2, Thioridazine 50-53-3,  
Chlorpromazine, biological studies 50-55-5, Reserpine 50-76-0,  
Actinomycin D 51-21-8, Fluorouracil 51-43-4, Epinephrine 52-39-1,  
Aldosterone 52-53-9, Verapamil 52-86-8, Haloperidol 53-79-2,  
Puromycin 56-54-2, Quinidine 57-22-7, Vincristine 57-27-2, Morphine,  
biological studies 57-41-0, Phenytoin 57-83-0, Progesterone,  
biological studies 58-32-2, Dipyrindamole 58-39-9, Perphenazine  
58-40-2, Promazine 58-89-9, Lindane 59-05-2, Methotrexate 60-57-1,  
Dieldrin 63-25-2, Carbaryl 64-85-7, Deoxycorticosterone 64-86-8,  
Colchicine 69-23-8, Fluphenazine 71-63-6, Digitoxin 72-43-5,  
Methoxychlor 72-57-1, Trypan\_blue 76-99-3, Methadone 83-43-2,

Methylprednisolone 83-60-3, Reserpine acid 85-79-0, Dibucaine  
 114-07-8, Erythromycin 115-29-7, Endosulfan 116-06-3, Aldicarb  
 117-89-5, Trifluoperazine 120-58-1, Isosafrole 130-95-0, Quinine  
 135-67-1, Phenoxazine 143-62-4, Digitoxigenin 146-48-5, Yohimbine  
 146-54-3, Triflupromazine 147-94-4, Cytarabine 148-82-3, Melphalan  
 152-58-9, Cortisolone 154-93-8, Carmustine 305-03-3, Chlorambucil  
 481-49-2, Cepharanthine 483-18-1, Emetine 485-71-2, Cinchonidine  
 518-28-5, Podophyllotoxin 569-61-9, Pararosaniline 732-11-6, Phosmet  
 749-02-0, Spiperone 865-21-4, Vinblastine 1095-90-5, Depridol  
 1622-62-4, Flunitrazepam 1646-88-4, Aldoxycarb 1672-46-4, Digoxigenin  
 1912-24-9, Atrazine 1951-25-3, Amiodarone 2001-95-8, Valinomycin  
 2032-59-9, Aminocarb 2182-14-1, Vindoline 2385-85-5, Mirex  
 2485-62-3, Cysteine methylester 2901-66-8, Methylreserpate 3690-10-6,  
 NSC309132 4375-07-9, Epipodophyllotoxin 4602-84-0, Farnesol  
 4685-14-7, Paraquat 5554-59-6, NSC364080 5602-68-6, NSC49899  
 7786-34-7, Mevinphos 10311-84-9, Dialifos 10540-29-1, Tamoxifen  
 13292-46-1, Rifampicin 15639-50-6, Safingol 16662-47-8, Gallopamil  
 17090-79-8, Monensin 18198-39-5, Tetraphenylphosphonium 18378-89-7,  
 Mithramycin 19186-35-7, Deoxypodophyllotoxin 19216-56-9, Prazosin  
 20278-59-5, NSC606532 20290-10-2, Morphine-6-glucuronide 20830-75-5,  
 Digoxin 20830-81-3, Daunomycin 21609-90-5, Leptophos  
**21829-25-4, Nifedipine** 23214-92-8, Doxorubicin  
 23491-52-3, HOE33342 23593-75-1, Clotrimazole 25316-40-9, Adriamycin  
 25953-19-9, Cefazolin 26644-46-2, Triforine 28380-24-7, Nigericin  
 29767-20-2, Teniposide 33069-62-4, Paclitaxel 33419-42-0, Etoposide  
 37517-30-9, Acebutolol 42399-41-7, Diltiazem 50471-44-8, Vinclozolin  
 50679-08-8, Terfenadine 53123-88-9, Rapamycin 53179-11-6, Loperamide  
 53772-82-0, Cis-Flupenthixol 55985-32-5, Nicardipine 56420-45-2,  
 Epirubicin 56980-93-9, Celiprolol 57808-66-9, Domperidone  
 58957-92-9, Idarubicin 59467-70-8, Midazolam 59865-13-3, Cyclosporin A  
 60207-90-1, Propiconazole 62893-19-0, Cefoperazone 62996-74-1,  
 Staurosporine 65271-80-9, Mitoxantrone 66085-59-4, Nimodipine  
 66358-49-4, NSC 314622 67642-36-8, NSC 268251 69712-56-7, Cefotetan  
 69806-50-4, Fluazifop-butyl 70288-86-7, Ivermectin 73113-90-3,  
 Hydroxyrubicin 75330-75-5, Lovastatin 75621-03-3, Chaps 75949-61-0,  
 Pafenolol 78186-34-2, Bisantrene 83799-24-0, Fexofenadine  
 89778-26-7, Toremifene 90523-31-2, Azidopine 99614-02-5, Ondansetron  
 114798-26-4, Losartan 114977-28-5, Docetaxel 120054-86-6,  
 Dexniguldipine **121263-19-2**, Calphostin C 121584-18-7, PSC833  
 123948-87-8, Topotecan 126463-15-8, NSC623083 127779-20-8, Saquinavir  
 128666-81-9, NSC686028 131246-38-3, NSC648403 135812-04-3, NSC 615985  
 137694-16-7, BIBW22 140945-01-3, S9788 142716-85-6, CP100356  
 143664-11-3, GF120918 150378-17-9, Indinavir 152044-53-6, Etoposide\_a  
 155213-67-5, Ritonavir 159875-50-0, NSC667533 159989-64-7, Nelfinavir  
 160450-56-6, NSC667532 161976-69-8, NSC666331 167465-36-3, LY335979  
 182198-53-4, L767679 191729-65-4, NSC678047 200340-45-0, NSC676593  
 208398-10-1, NSC676610 208398-12-3, NSC676615 208398-21-4, NSC676618  
 208398-22-5, NSC676617 208398-24-7, NSC676616 432550-02-2, NSC617286  
 432550-03-3, NSC630148 432550-04-4, NSC630721 432550-05-5, NSC 633528  
 432550-06-6, NSC664565 432550-08-8, NSC668354 432550-09-9, NSC674508  
 432550-10-2, NSC 674570 432550-22-6, NSC630357 432550-23-7, NSC639677  
 432550-24-8, NSC653278 432550-25-9, NSC667551 432550-26-0, NSC667560  
 432550-27-1, NSC671400 717849-72-4 717849-74-6 718637-11-7, NSC  
 667558 718637-12-8, NSC 676602

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
 (Biological study); USES (Uses)

(prediction of P-glycoprotein substrates by support vector machine  
 approach)

IT **21829-25-4, Nifedipine 121263-19-2, Calphostin**

C

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
 (Biological study); USES (Uses)

(prediction of P-glycoprotein substrates by support vector machine

Cc1c(C(=O)OC)c(Cc2ccccc2[N+](=O)[O-])c(C)c1NCOc1c(O)c2c3c(c1)c(O)c(OC)c2C(=O)C(OC)C3C(=O)C(OC)C(COC(=O)c4ccc(O)cc4)C(C)OC(=O)c5ccccc5

L11 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN  
ACCESSION NUMBER: 2002:227327 CAPLUS  
DOCUMENT NUMBER: 137:148  
TITLE: A Computational Ensemble Pharmacophore Model for  
Identifying Substrates of P-Glycoprotein  
AUTHOR(S): Penzotti, Julie E.; Lamb, Michelle L.; Evensen, Erik;  
Grootenhuys, Peter D. J.  
CORPORATE SOURCE: Deltagen Research Laboratories, San Diego, CA, 92121,  
USA  
SOURCE: Journal of Medicinal Chemistry (2002), 45(9),  
1737-1740  
CODEN: JMCMAR; ISSN: 0022-2623  
PUBLISHER: American Chemical Society  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB P-glycoprotein (P-gp) functions as a drug efflux pump, mediating multidrug resistance and limiting the efficacy of many drugs. Clearly, identification of potential P-gp substrate liability early in the drug discovery process would be advantageous. We describe a multiple-pharmacophore model that can discriminate between substrates and nonsubstrates of P-gp with an accuracy of 63%. The application of this filter allows large virtual libraries to be screened efficiently for compds. less likely to be transported by P-gp.

IT Conformation  
Drug screening  
Multidrug resistance  
Pharmacophores  
Simulation and Modeling  
(computational ensemble pharmacophore model for identifying substrates of P-glycoprotein)

IT P-glycoproteins  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(computational ensemble pharmacophore model for identifying substrates of P-glycoprotein)

IT Chemistry  
(computational; computational ensemble pharmacophore model for identifying substrates of P-glycoprotein)

IT Biological transport  
(drug; computational ensemble pharmacophore model for identifying substrates of P-glycoprotein)

IT Biological transport  
(efflux; computational ensemble pharmacophore model for identifying substrates of P-glycoprotein)

IT 73113-90-3, Hydroxyrubicin  
RL: PRP (Properties)  
(Hydroxyrubicin; computational ensemble pharmacophore model for identifying substrates of P-glycoprotein)

IT 50-02-2, DEXAMETHASONE 50-06-6, PHENOBARBITAL, properties 50-07-7, MITOMYCIN C 50-18-0, CYCLOPHOSPHAMIDE 50-22-6, CORTICOSTERONE 50-23-7, HYDROCORTISONE 50-24-8, PREDNISOLONE 50-27-1, ESTRIOL 50-52-2, THIORIDAZINE 50-55-5, RESERPINE 50-76-0, Actinomycin D 51-21-8, FLUOROURACIL 51-43-4, EPINEPHRINE 52-39-1, ALDOSTERONE 52-53-9, VERAPAMIL 53-79-2, PUROMYCIN 56-54-2, QUINIDINE 57-22-7, VINCRISTINE 57-41-0, PHENYTOIN 57-83-0, PROGESTERONE, properties 58-39-9, PERPHENAZINE 58-89-9, LINDANE 60-57-1, DIELDRIN 63-25-2, CARBARYL 64-85-7, DEOXYcorticosterone 64-86-8, Colchicine 69-23-8, FLUPHENAZINE 71-63-6, DIGITOXIN 72-43-5, METHOXYCHLOR 72-57-1, TRYPAN BLUE 76-99-3, METHADONE 83-43-2, METHYLPREDNISOLONE 83-60-3, Reserpine acid 85-79-0, DIBUCAINE 114-07-8, ERYTHROMYCIN 115-29-7, ENDOSULFAN\* 116-06-3, ALDICARB 117-89-5, TRIFLUOPERAZINE 120-58-1, ISOSAFROLE 130-95-0, QUININE 135-67-1, PHENOXAZINE 143-62-4, DIGITOXIGENIN 146-48-5, YOHIMBINE 146-54-3, TRIFLUPROMAZINE 147-94-4, CYTARABINE 148-82-3, MELPHALAN 152-58-9, CORTEXOLONE 154-93-8, CARMUSTINE 305-03-3, CHLORAMBUCIL 481-49-2, CEPHARANTHINE 485-71-2, CINCHONIDINE 732-11-6, PHOSMET 749-02-0, SPIPERONE 865-21-4, VINBLASTINE 1646-88-4, ALDOXYCARB 1672-46-4, DIGOXIGENIN 1912-24-9, ATRAZINE 1951-25-3, Amiodarone 2001-95-8, Valinomycin 2182-14-1, VINDOLINE 2385-85-5, MIREX 2468-21-5 2709-56-0, FLUPENTHIXOL 2751-90-8, TETRAPHENYL PHOSPHONIUM BROMIDE 2901-66-8, METHYLRESERPATE 3131-03-1, PRISTINAMYCIN 3690-10-6, NSC 309132 4375-07-9, EPIPODOPHYLLOTOXIN 4602-84-0, FARNESOL 4685-14-7, PARAQUAT 5554-59-6, NSC 364080 5602-68-6, NSC 49899 7786-34-7, MEVINPHOS 10311-84-9, DIALIFOS 10540-29-1, TAMOXIFEN 13292-46-1, RIFAMPICIN 15639-50-6, SAFINGOL 16662-47-8, GALLOPAMIL 17090-79-8, MONENSIN 18378-89-7, MITHRAMYCIN A 19186-35-7, DEOXY-PODOPHYLLOTOXIN 19216-56-9, PRAZOSIN 20278-59-5, NSC 606532 20290-10-2, MORPHINE 6-GLUCURONIDE 20830-75-5, DIGOXIN 20830-81-3, DAUNORUBICIN 21609-90-5, LEPTOPHOS 21829-25-4, NIFEDIPINE

23214-92-8, DOXORUBICIN 23491-52-3, HOE33342 23593-75-1, CLOTRIMAZOLE  
 25953-19-9, CEFAZOLIN 26644-46-2, TRIFORINE 28380-24-7, Nigericin  
 29767-20-2, TENIPOSIDE 33069-62-4, PACLITAXEL 33419-42-0, ETOPOSIDE  
 37517-30-9, ACEBUTOLOL 41575-94-4, CARBOPLATIN 42399-41-7, DILTIAZEM  
 44641-43-2, CYSTEINE methyl ESTER 50471-44-8, VINCLOZOLIN 50679-08-8,  
 TERFENADINE 53123-88-9, RAPAMYCIN 53179-11-6, LOPERAMIDE 53772-82-0,  
 cis-Flupenthixol 55123-66-5, LEUPEPTIN 55985-32-5, NICARDIPINE  
 56980-93-9, CELIPROLOL 58957-92-9, IDARUBICIN 59467-70-8, MIDAZOLAM  
 59865-13-3, Cyclosporin A 60207-90-1, PROPICONAZOLE 62669-70-9,  
 RHODAMINE 123 62893-19-0, CEFOPERAZONE 62996-74-1, STAUROSPORINE  
 64706-54-3, BEPRIDIL 65271-80-9, MITOXANTRONE 66085-59-4, NIMODIPINE  
 66358-49-4, NSC 314622 67642-36-8 68000-92-0 69712-56-7, CEFOTETAN  
 69806-50-4, FLUAZIFOPBUTYL 70288-86-7, IVERMECTIN 75330-75-5,  
 LOVASTATIN 75621-03-3, CHAPS 75949-61-0, PAFENOLOL 78186-34-2,  
 BISANTRENE 89778-26-7, TOREMIFENE 90523-31-2, AZIDOPINE 99614-02-5,  
 ONDANSETRON 114977-28-5, DOCETAXEL 120054-86-6, DEXNIGULDIPINE  
 120685-11-2, CG P-41251 **121263-19-2**, CALPHOSTIN C 121584-18-7,  
 SDZ PSC-833 123948-87-8, TOPOTECAN 126463-15-8, NSC 623083  
 127779-20-8, SAQUINAVIR 128666-81-9, NSC 686028 130062-64-5  
 131246-38-3, NSC 648403 135812-04-3, NSC 615985 137694-16-7, BIBW 22BS  
 140945-01-3, S 9788 143664-11-3, GF 120918 150378-17-9, INDINAVIR  
 152044-53-6, EPOTHILONE A 155252-35-0 155252-36-1 159875-50-0, NSC  
 667533 159989-64-7, NELFINAVIR 160450-56-6, NSC 667532 161976-69-8,  
 NSC 666331 164665-13-8 167465-36-3, LY335979 182198-53-4, L-767679  
 191729-65-4, NSC 678047 200340-45-0, NSC 676593 208398-10-1, NSC  
 676610 208398-12-3, NSC 676615 208398-21-4, NSC 676618 208398-22-5,  
 NSC 676617 208398-24-7, NSC 676616 210365-50-7 210365-51-8  
 210365-55-2 210365-56-3 211060-81-0 432041-70-8 432550-02-2, NSC  
 617286 432550-03-3, NSC 630148 432550-04-4, NSC 630721 432550-05-5  
 432550-06-6, NSC 664565 432550-08-8, NSC 668354 432550-09-9, NSC  
 674508 432550-10-2 432550-22-6, NSC 630357 432550-23-7, NSC 639677  
 432550-24-8, NSC 653278 432550-25-9, NSC 667551 432550-26-0, NSC  
 667560 432550-27-1, NSC 671400

RL: PRP (Properties)

(computational ensemble pharmacophore model for identifying substrates  
 of P-glycoprotein)

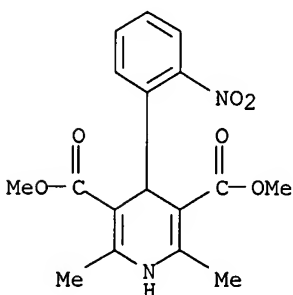
IT **21829-25-4, NIFEDIPINE 121263-19-2, CALPHOSTIN**  
 C

RL: PRP (Properties)

(computational ensemble pharmacophore model for identifying substrates  
 of P-glycoprotein)

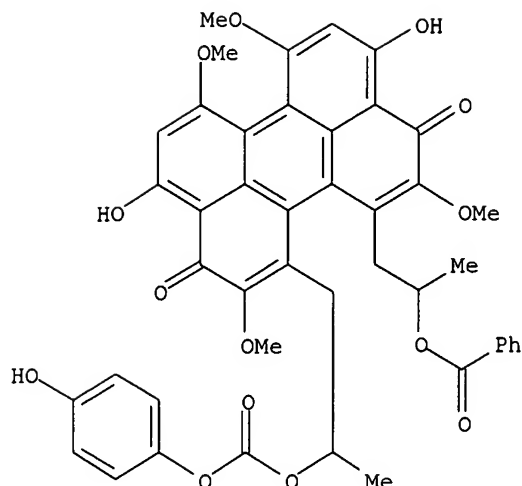
RN 21829-25-4 CAPLUS

CN 3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-  
 , dimethyl ester (9CI) (CA INDEX NAME)



RN 121263-19-2 CAPLUS

CN Carbonic acid, (1R)-2-[12-[(2R)-2-(benzoyloxy)propyl]-3,10-dihydro-4,9-  
 dihydroxy-2,6,7,11-tetramethoxy-3,10-dioxo-1-perylenyl]-1-methylethyl  
 4-hydroxyphenyl ester, stereoisomer (9CI) (CA INDEX NAME)



REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1998:132450 CAPLUS

DOCUMENT NUMBER: 128:252560

TITLE: Internalization of *Aeromonas hydrophila* by fish epithelial cells can be inhibited with a tyrosine kinase inhibitor

AUTHOR(S): Tan, E.; Low, K. W.; Wong, W. S. F.; Leung, K. Y.

CORPORATE SOURCE: School of Biological Sciences, Faculty of Science, National University of Singapore, Singapore, 119260, Singapore

SOURCE: Microbiology (Reading, United Kingdom) (1998), 144(2), 299-307

CODEN: MROBEO; ISSN: 1350-0872

PUBLISHER: Society for General Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB *Aeromonas hydrophila* is a Gram-neg. bacterium that is pathogenic in fish by causing motile aeromonadic septicemia. It can enter (invade) fish cells and survive as an intracellular parasite. The host-pathogen interaction and signal transduction pathway were studied by screening signal transduction inhibitors using carp epithelioma papillosum cells (EPC) and a virulent strain of the bacterium, PPD134/91. Genistein, a tyrosine kinase inhibitor, delayed the internalization of *A. hydrophila* into host cells, suggesting that tyrosine phosphorylation plays a role in the internalization process. Staurosporine, a protein kinase C inhibitor, and sodium orthovanadate, a protein tyrosine phosphatase inhibitor, accelerated the internalization. Other virulent strains of *A. hydrophila* were also examined. It is likely that all strains, irrespectively of their serogroups, use the same signalling pathway to facilitate the bacterial uptake by cells.

IT Actins

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(F-; genistein effects on *Aeromonas hydrophila* internalization by fish epithelial cells)

IT *Aeromonas hydrophila*

Epithelium

(genistein effects on *Aeromonas hydrophila* internalization by fish

epithelial cells)

IT Biological transport  
(internalization; genistein effects on *Aeromonas hydrophila*  
internalization by fish epithelial cells)

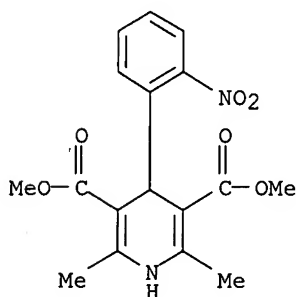
IT Cytotoxic agents  
(tyrphostins; genistein effects on *Aeromonas hydrophila* internalization  
by fish epithelial cells)

IT 152-11-4, Verapamil hydrochloride 446-72-0, Genistein 486-66-8,  
Daidzein 13721-39-6, Sodium orthovanadate **21829-25-4**,  
**Nifedipine** 62996-74-1, Staurosporine 70563-58-5, Herbimycin a  
78111-17-8, Okadaic acid 101932-71-2, Calyculin a 118409-60-2,  
Tyrphostin 47 **121263-19-2**, Calphostin c  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological  
study, unclassified); BIOL (Biological study)  
(genistein effects on *Aeromonas hydrophila* internalization by fish  
epithelial cells)

IT **21829-25-4**, **Nifedipine** **121263-19-2**, Calphostin  
c  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological  
study, unclassified); BIOL (Biological study)  
(genistein effects on *Aeromonas hydrophila* internalization by fish  
epithelial cells)

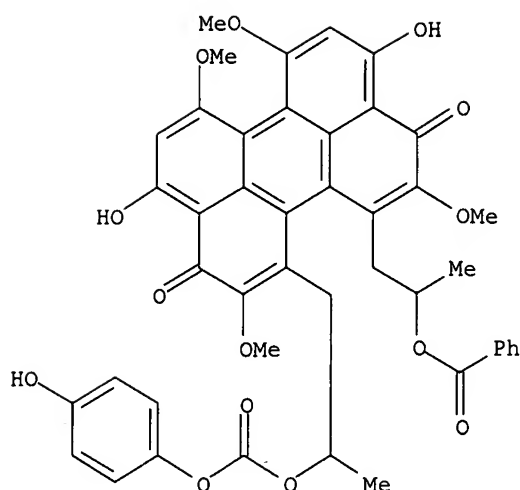
RN 21829-25-4 CAPLUS

CN 3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-  
, dimethyl ester (9CI) (CA INDEX NAME)



RN 121263-19-2 CAPLUS

CN Carbonic acid, (1R)-2-[12-[(2R)-2-(benzoyloxy)propyl]-3,10-dihydro-4,9-  
dihydroxy-2,6,7,11-tetramethoxy-3,10-dioxo-1-perylenyl]-1-methylethyl  
4-hydroxyphenyl ester, stereoisomer (9CI) (CA INDEX NAME)



REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:113253 CAPLUS

DOCUMENT NUMBER: 142:309808

TITLE: Effect of emodin on motility signal transduction in colonic smooth muscle cells in rats with multiple organ dysfunction syndrome

AUTHOR(S): Chen, Zhe-yu; Qi, Qing-hui; Ma, Tao; Jian, Xu  
CORPORATE SOURCE: The West China Hospital, Sichuan University, Chengdu, 610041, Peop. Rep. China

SOURCE: Zhongguo Zhongxiyi Jiehe Zazhi (2004), 24(12), 1106-1109

CODEN: ZZJZAS; ISSN: 1003-5370

PUBLISHER: Zhongguo Zhongxiyi Jiehe Zazhi Bianjibu

DOCUMENT TYPE: Journal

LANGUAGE: Chinese

AB Objective: To observe the effect of emodin on motility signal transduction and calcium ion in colonic smooth muscle cells (SMC) in rats with bacterial peritonitis caused multiple organ dysfunction syndrome (MODS). Methods: Observation was conducted in colon of MODS model rats on (1) effects of emodin on the contraction of muscular strip and cells of colonic smooth muscle, and influences of specific myoglobin light chain kinase inhibitor (ML-7) and selective protein kinase C inhibitor (Calphostin C) on these effects; and (2) effect of emodin on calcium ion in SMC. Results: Emodin could directly contract the muscular strip and cells of smooth muscle; ML-7 and Calphostin could inhibit these contractile action to some extent. Under MODS condition, emodin could still increase the intracellular calcium ion concentration; this effect could

be

inhibited by heparin (inosamine triphosphate receptor inhibitor) IP3 and ryanodine receptor inhibitor in MODS model but the calcium chelator EGTA and nifedipine (the specific cell membrane voltage dependent calcium channel blocker) showed no influence on it. Conclusion: Emodin could directly contract the colonic smooth muscle in MODS model rats, which is mediated by raise the signal path MLCK of calcium ion and the PKC $\alpha$  path for increase calcium sensibility. The mechanism of increasing calcium ion is mainly through IP3 and RyR the two calcium ion channel receptor in the sarcoplasm.

IT Intestine

(colon; emodin effect on motility signal transduction in colonic smooth muscle cells in rats with multiple organ dysfunction syndrome)

IT Cell migration  
(colonic smooth muscle; emodin effect on motility signal transduction in colonic smooth muscle cells in rats with multiple organ dysfunction syndrome)

IT Multiple organ failure  
Signal transduction, biological  
(emodin effect on motility signal transduction in colonic smooth muscle cells in rats with multiple organ dysfunction syndrome)

IT Calcium channel  
Inositol 1,4,5-trisphosphate receptors  
Ryanodine receptors  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(emodin effect on motility signal transduction in colonic smooth muscle cells in rats with multiple organ dysfunction syndrome)

IT Inflammation  
Peritoneum, disease  
(peritonitis, bacterial; emodin effect on motility signal transduction in colonic smooth muscle cells in rats with multiple organ dysfunction syndrome)

IT Cytoplasm  
(sarcoplasm; emodin effect on motility signal transduction in colonic smooth muscle cells in rats with multiple organ dysfunction syndrome)

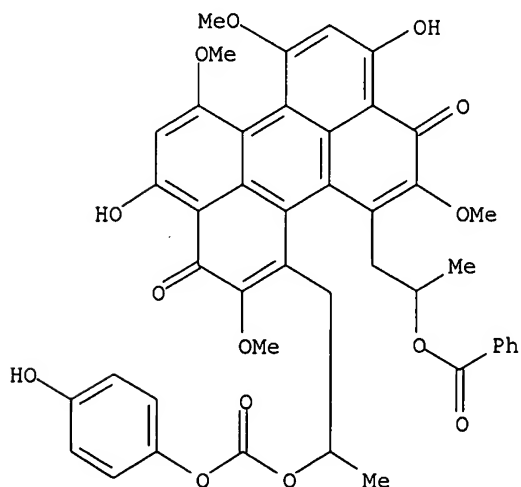
IT Muscle  
(smooth; emodin effect on motility signal transduction in colonic smooth muscle cells in rats with multiple organ dysfunction syndrome)

IT 14127-61-8, Calcium ion, biological studies 109376-83-2, ML-7  
121263-19-2, Calphostin C  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(emodin effect on motility signal transduction in colonic smooth muscle cells in rats with multiple organ dysfunction syndrome)

IT 121263-19-2, Calphostin C  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(emodin effect on motility signal transduction in colonic smooth muscle cells in rats with multiple organ dysfunction syndrome)

RN 121263-19-2 CAPLUS

CN Carbonic acid, (1R)-2-[12-[(2R)-2-(benzoyloxy)propyl]-3,10-dihydro-4,9-dihydroxy-2,6,7,11-tetramethoxy-3,10-dioxo-1-perylenyl]-1-methylethyl 4-hydroxyphenyl ester, stereoisomer (9CI) (CA INDEX NAME)



=> SET TERMSET E#

SET COMMAND COMPLETED

=> DEL SEL Y

=> SEL L1 1 RN

E1 THROUGH E1 ASSIGNED

=> S E1/RN

L3 1 121263-19-2/RN

=> SET TERMSET LOGIN

SET COMMAND COMPLETED

=> FIL NAPRALERT

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.52	29.80

FILE 'NAPRALERT' ENTERED AT 12:52:22 ON 28 AUG 2006  
COPYRIGHT (C) 2006 Board of Trustees of the University of Illinois,  
University of Illinois at Chicago.

FILE COVERS 1650 TO 8 AUG 2005 (20050808/ED)

This file contains CAS Registry Numbers for easy and accurate  
substance identification.

\*\*\*\*\* The NAPRALERT File is no longer being updated. \*\*\*\*\*

=> S L3

L4 5 L3

=> file caplus biosis embase

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.73	30.53

FILE 'CAPLUS' ENTERED AT 12:52:43 ON 28 AUG 2006  
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.  
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.  
COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'BIOSIS' ENTERED AT 12:52:43 ON 28 AUG 2006  
Copyright (c) 2006 The Thomson Corporation

FILE 'EMBASE' ENTERED AT 12:52:43 ON 28 AUG 2006  
Copyright (c) 2006 Elsevier B.V. All rights reserved.

=> file reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	2.76	33.29

FILE 'REGISTRY' ENTERED AT 12:53:47 ON 28 AUG 2006  
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.  
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.  
COPYRIGHT (C) 2006 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file  
provided by InfoChem.

STRUCTURE FILE UPDATES: 27 AUG 2006 HIGHEST RN 904741-41-9  
DICTIONARY FILE UPDATES: 27 AUG 2006 HIGHEST RN 904741-41-9

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH June 30, 2006

Please note that search-term pricing does apply when  
conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and  
predicted properties as well as tags indicating availability of  
experimental property data in the original document. For information  
on property searching in REGISTRY, refer to:

<http://www.cas.org/ONLINE/UG/regprops.html>

=> s procardia  
L5 1 PROCARDIA

=> d

L15 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:124725 CAPLUS

DOCUMENT NUMBER: 140:178861

TITLE: Calphostin-C Induction of Vascular Smooth Muscle Cell Apoptosis Proceeds through Phospholipase D and Microtubule Inhibition

AUTHOR(S): Zheng, Xi-Long; Gui, Yu; Du, Guangwei; Frohman, Michael A.; Peng, Dao-Quan

CORPORATE SOURCE: Department of Biochemistry & Molecular Biology, Smooth Muscle Research Group, University of Calgary, Calgary, AB, T2N 4N1, Can.

SOURCE: Journal of Biological Chemistry (2004), 279(8), 7112-7118

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Calphostin-C, a protein kinase C inhibitor, induces apoptosis of cultured vascular smooth muscle cells. However, the mechanisms are not completely defined. Because apoptosis of vascular smooth muscle cells is critical in several proliferating vascular diseases such as atherosclerosis and restenosis after **angioplasty**, we decided to investigate the mechanisms underlying the calphostin-C-induced apoptotic pathway. We show here that apoptosis is inhibited by the addition of exogenous phosphatidic acid, a metabolite of phospholipase D (PLD), and that calphostin-C inhibits completely the activities of both isoforms of PLD, PLD1 and PLD2. Overexpression of either PLD1 or PLD2 prevented the vascular smooth muscle cell apoptosis induced by serum withdrawal but not the calphostin-C-elicited apoptosis. These data suggest that PLDs have anti-apoptotic effects and that complete inhibition of PLD activity by calphostin-C induces smooth muscle cell apoptosis. We also report that calphostin-C induced microtubule disruption and that the addition of exogenous phosphatidic acid inhibits calphostin-C effects on microtubules, suggesting a role for PLD in stabilizing the microtubule network. Overexpressing PLD2 in Chinese hamster ovary cells phenocopies this result, providing strong support for the hypothesis. Finally, taxol, a microtubule stabilizer, not only inhibited the calphostin-C-induced microtubule disruption but also inhibited apoptosis. We therefore conclude that calphostin-C induces apoptosis of cultured vascular smooth muscle cells through inhibiting PLD activity and subsequent microtubule polymerization

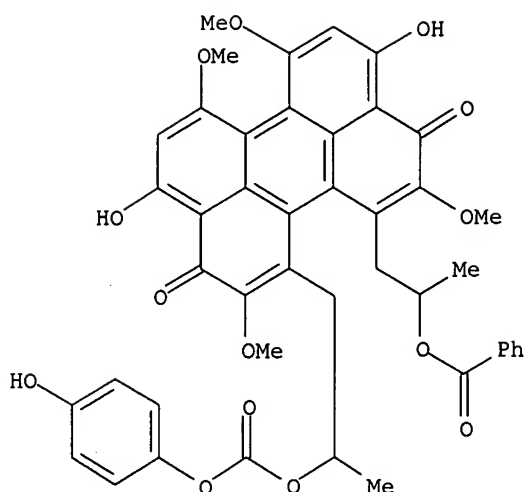
IT 121263-19-2, Calphostin-C

RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)

(calphostin-C induction of vascular smooth muscle cell apoptosis proceeds through phospholipase D and microtubule inhibition)

RN 121263-19-2 CAPLUS

CN Carbonic acid, (1R)-2-[12-[(2R)-2-(benzoyloxy)propyl]-3,10-dihydro-4,9-dihydroxy-2,6,7,11-tetramethoxy-3,10-dioxo-1-perylenyl]-1-methylethyl 4-hydroxyphenyl ester, stereoisomer (9CI) (CA INDEX NAME)



REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 2 OF 2 USPATFULL on STN  
 ACCESSION NUMBER: 2002:262057 USPATFULL  
 TITLE: Agents for the prevention of damages caused by stress conditions  
 INVENTOR(S): Bar-Shavit, Rachel, Jerusalem, ISRAEL  
 PATENT ASSIGNEE(S): Hadasit Medical Research Services & Development Limited, Jerusalem, ISRAEL (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6461611	B1	20021008
	WO 9942483		19990826
APPLICATION INFO.:	US 2000-600031		20000720 (9)
	WO 1999-IL95		19990216
			20000720 PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	IL 1998-123349	19980218
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	GRANTED	
PRIMARY EXAMINER:	Tate, Christopher R.	
ASSISTANT EXAMINER:	Winston, Randall	
LEGAL REPRESENTATIVE:	Oliff & Berridge, PLC	
NUMBER OF CLAIMS:	5	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	7 Drawing Figure(s); 7 Drawing Page(s)	
LINE COUNT:	634	

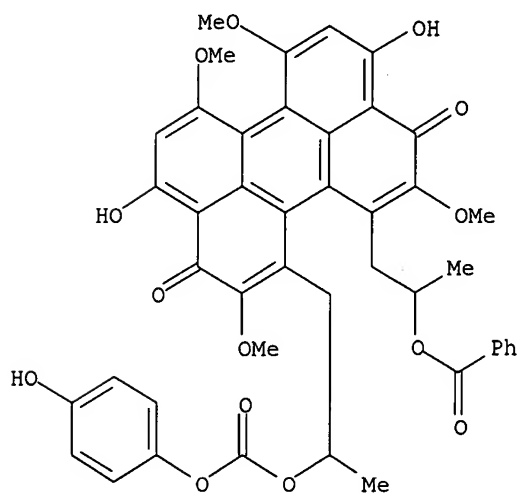
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Pharmaceutical compositions for the treatment of a decrease in the levels of protease activated receptor (PAR) mRNA caused by a lack or decrease of oxygen level and/or a lack or decrease of blood flow including pharmaceutically acceptable carriers and activators of PAR are provided. Methods for prevention of a decrease in the levels of protease-activated receptor PAR mRNA caused by lack or decrease in the oxygen level and/or lack or decrease in blood flow are also provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT 121263-19-2, Calphostin C  
 (protease-activated receptor (PAR) activators for prevention of damage

caused by stress conditions such as hypoxia or ischemia)  
RN 121263-19-2 USPATFULL  
CN Carbonic acid, (1R)-2-[12-[(2R)-2-(benzoyloxy)propyl]-3,10-dihydro-4,9-dihydroxy-2,6,7,11-tetramethoxy-3,10-dioxo-1-perylenyl]-1-methylethyl 4-hydroxyphenyl ester, stereoisomer (9CI) (CA INDEX NAME)



=>